

A research agenda for moving early medical pregnancy termination over the counter

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Given the overall safety profile and increasing availability of medical pregnancy termination drugs, we asked: would the mifepristone–misoprostol regimen for medical termination at ≤ 10 weeks of gestation meet US Food and Drug Administration regulatory criteria for over-the-counter (OTC) approval, and if not, what are the present research gaps? We conducted a literature review of consumer behaviours necessary for a successful OTC application for medical termination at ≤ 10 weeks of gestation and identified crucial research gaps. If we were to embark on a development programme for OTC or more generally, self-use of medical termination, the critical elements missing are the label comprehension, self-selection and actual use studies.

Keywords First trimester, medical termination of pregnancy, mifepristone, misoprostol, pregnancy termination, over-the-counter.

Tweetable abstract Considering medical pregnancy termination through the over-the-counter regulatory lens clarifies critical evidence gaps.

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Background

Medical pregnancy termination with mifepristone and misoprostol within the first 10 weeks of pregnancy is safe and highly effective. Serious complications are rare. The few contraindications are generally determined through a review of a woman's medical history and physical examination, without requiring laboratory testing. Gestational age eligibility is based on the woman's last menstrual period in combination with an examination or, if necessary, ultrasonography.¹ Administration of the misoprostol and pregnancy expulsion usually take place outside a health facility and women manage the termination process at home, similar to experiencing a spontaneous termination of pregnancy. Confirming that early termination is successful has traditionally taken place in a health facility 1–2 weeks later and is based on history and physical examination and, if needed, ultrasound or laboratory testing.^{2,3} Although home use of semi-quantitative or low-sensitivity urine pregnancy tests has also been shown to be effective in research studies to detect a rare ongoing pregnancy, they are not universally available.^{2–4} Given the effectiveness of the

regimen and inconvenience of in-clinic visits, the World Health Organization recommends that routine follow up after mifepristone/ misoprostol termination is not necessary if a woman has adequate information about when to seek care for complications and how to meet her contraceptive needs.⁵

Increasingly, women are obtaining abortifacient medicines through non-traditional routes including pharmacies, drug sellers, and online or telemedicine services.^{6–10} These avenues are most commonly used in settings where termination services are restricted or access is difficult.¹¹ They may also reflect the way some women prefer to access pregnancy termination care; however, this has not been studied, particularly where women have the option of accessible, clinic-based high-quality services. In settings where mifepristone is not available, women may still access misoprostol. Success rates following misoprostol only are lower than the combination of mifepristone and misoprostol; however, this is a safe termination option when mifepristone is not available.¹² As misoprostol alone is less effective and follow up is therefore recommended, this review focuses only on the combination regimen.

Given the overall safety of the early pregnancy termination process, and the various ways women are obtaining medical termination drugs and using them independently, we were interested in assessing from the literature the question: would the mifepristone–misoprostol regimen for medical termination at ≤ 10 weeks of gestation meet US Food and Drug Administration (FDA) regulatory criteria for over-the-counter (OTC) approval, and if not, what are the present research gaps?

Methods

We evaluated women's self-use of medical pregnancy termination using the framework of a medicine application to the US FDA for OTC use. In an application for this regulatory status, medicines must have an acceptable toxicity profile, be unlikely to be addictive and have a low abuse potential. In addition, a series of investigations need to demonstrate that consumers can appropriately, and therefore safely, use the medicine without medical supervision. Behaviours to be demonstrated by the consumer to indicate safe use outside medical supervision include: ability to self-diagnose for the treatment indication, self-screen for eligibility and contraindications based on label instructions (self-selection), comprehension of written instructions (label comprehension), and knowledge of when to seek medical care for complications or side effects (actual use). Finally, the benefit–risk profile must be considered sufficiently positive to provide medicines without medical supervision.

We conducted a review of the peer-reviewed literature looking at consumer behaviours that would be necessary for an OTC application for medical pregnancy termination ≤ 10 weeks of gestation. Namely, demonstration of a woman's ability to self-screen for eligibility and contraindications, comprehension of written instructions on how to use, and knowledge of when to seek medical care for complications. We included studies published since the year 2000 investigating mifepristone and misoprostol termination. Studies were excluded if the behaviour was not ascertained independent of a clinician or health worker. We focused on behaviours associated with correct use and did not explore the potential for abuse.

We accept that women can self-diagnose the condition of pregnancy as this is generally the case among women seeking termination and is independent of OTC status. An additional step for OTC pregnancy termination with mifepristone in the USA would require removal of the outdated Risk Evaluation and Mitigation Strategy in the USA for Mifeprex, which was meant to ensure the benefits of use outweigh the risks; calls for its removal have been published elsewhere.¹³

Studies were included in the review if they investigated one of the consumer behaviours required for appropriate

use (described below) of mifepristone–misoprostol termination where a woman is performing the task independently. The behaviours necessary for obtaining a medical pregnancy termination safely and effectively were identified by the authors as: (1) assessing gestational age as eligible, (2) identifying eligibility for the medicines, (3) self-administering the medications according to instructions, and (4) identifying complications or need to seek medical care, including for ongoing pregnancy. Because medical termination later in pregnancy involves different regimens and usually is performed in a health facility, we limited our review to termination at ≤ 10 weeks gestation.

Results

Assessing gestational age (≤ 10 weeks LMP) eligibility for medical pregnancy termination

Gestational age assessment before undergoing medical pregnancy termination is necessary to ensure women take the recommended dose and regimen of medications, and in the appropriate setting. Because of increasing uterine sensitivity to misoprostol with advancing gestational age, regimens for medical termination change in the late first trimester and second trimester to repeated, lower doses of misoprostol. Termination later in pregnancy also carries increasing medical risks and, potentially, legal and social risks, depending on the setting. The woman's experience may also be more painful, and acceptability for home expulsion may be lower.

Clinically, gestational age can be assessed to determine eligibility for medical termination using a woman's last menstrual period (LMP) in combination with physical examination by a trained provider; ultrasound may be used when gestational age is not clear, or pregnancy location or viability is in question. However, accumulating evidence indicates that many women can determine the duration of their pregnancy based on their LMP. Most women can recall their LMP regardless of education or whether or not they routinely record their LMP dates.^{1,14,15} A 2014 systematic review evaluating the accuracy of using LMP alone to assess gestational age before early medical termination included five studies of fair to poor quality, reporting data for more than 7500 women.¹⁶ Overall, between 3 and 12% of women eligible for medical termination based on their LMP were actually ineligible when evaluated by ultrasound dating. A secondary analysis of these data¹⁷ specifically examined at which week by LMP dating women would be both eligible and unlikely to underestimate gestational age (Table 1). Of 2681 women who were confident of an LMP < 56 days, only 16 (0.6%) actually had a gestational age > 70 days and would have been incorrectly considered eligible for medical termination, from the data of the largest study included in the review.¹ In the smaller included

Table 1. How women can self-assess gestational age eligibility in varying contexts

Setting	What women can do	Results	Population/ Source
Research study at termination clinics	Assess whether last menstrual period was certain to have been within 56 days	99% correctly identified as being eligible (<70 days) if their last menstrual period was certain to have been <56 days prior 0.6% >70 days	Studies from UK/ USA Most data from women seeking medical termination at ten sites in USA ¹ Raymond 2015: combined data from three studies ¹⁷
Telemedicine: seeking medical termination drugs online (restrictions on service availability in country)	Assess if within 63 days (by obtaining an ultrasound or by last menstrual period) 74–82% had ultrasound for dating	All were within 63 days When followed up (83%), not all women were eligible (<63 days): 67% were <63 days 23% were 70–84 days 10% were ≥13 weeks	Global data ⁸ Brazil ⁷

studies, this proportion is higher (7–12%). Authors concluded that LMP alone is a promising alternative to determine gestational age, but requires further research if women are to assess eligibility independently.^{16,17}

Outside the research setting, women who seek and receive medical pregnancy termination through telemedicine services such as Women on Web (www.womenonweb.org) are asked by the service to obtain ultrasound examinations to ensure their eligibility. In reports describing these services, most women obtained an ultrasound for gestational age dating but approximately one-third who were followed up after receiving treatment had pregnancies which were of 10 weeks of gestation or greater by ultrasound.^{7,8}

Assessment of gestational age by LMP may be aided by technologies. Recent research evaluated a mobile phone application for gestational age dating, piloted in Ghana, but adaptable for use globally: in this study, women assessed gestational age using LMP with the mobile phone application. Although the majority (94%) were in agreement with the providers that their gestational age was <13 weeks, 72% of women needed verbal instructions from the interviewer to use the application's pregnancy wheel to complete the assessment.¹⁸ Of those who had pregnancies >13 weeks, most (83%) were between 13 and 16 weeks, and the remaining women ranged between 18 and 28 weeks of gestation.

In a similar study, 71/78 (91%) participants in South Africa found an online gestational age calculator easy to use, although a research assistant was present to answer questions.¹⁹ Large variances in self-calculated gestational age when compared with ultrasound were observed. On average, women overestimated gestational age by 0.5 days (SD 14.5). In this small sample, 4% (3/78) self-assessed as eligible for medical termination, whereas ultrasound dating deemed them ineligible (>63 days).

Assessing other eligibility criteria for medicines

No label comprehension studies have been performed for the mifepristone and misoprostol regimen. This step would be included as standard in an application to the FDA to change the legal status of a drug from prescription to OTC as the label should provide the important information about its use in the absence of a clinician's explanation.²⁰ A label comprehension study assesses the extent to which consumers understand the information on the labelling and are then able to apply the information when making decisions about use of the drug in a hypothetical situation. Data derived from a label comprehension study can identify messages that require a clearer presentation of important information.²⁰ These studies generally rely on comprehension levels assessed for each important message, with label wording modified iteratively until comprehension meets an acceptable, predefined range.

Online services such as Women on Web provide yes or no screening questions that are reviewed by a physician.^{7,8} In a study using an eligibility checklist in Nepal among 2723 women who completed the checklist, there was a 71% agreement between women's interpretation of their responses and their eligibility as determined by the checklist;²¹ most of those not in agreement had determined themselves to be eligible when, in fact, they were not.

Ability to self-administer mifepristone and misoprostol outside the clinic

Multiple studies demonstrate that women can administer misoprostol at home after mifepristone received in the clinic with similar effectiveness and greater satisfaction for those who choose it than misoprostol administration in the clinic.²² Newer data demonstrate that women can take both medicines of the regimen (mifepristone followed by misoprostol) after determining eligibility and receiving

instructions from a healthcare provider in person,^{23–26} or online/ by email.^{7,8} Consequently, the Mifeprex label (Danco Laboratories, New York City, NY, USA) has recently been updated to allow for the regimen to be self-administered in the setting of a woman's choosing.²⁷

The ability for a woman to effectively administer these medications following instructions on how to do so appears to be well-established. Women's ability to follow instructions on how to use the medicines purely based on written instructions on the label has not been investigated.

Identifying when to seek medical care

No studies of complication rates following self-use of medical pregnancy termination completely outside the health system, such as would be assessed in an actual use study, have been published. An actual use study, wherein use of the drug in a simulated OTC setting and behaviours surrounding use (including appropriate use for the indication, seeking care for complications), is generally a necessary step before a product is launched OTC. This type of study demonstrates that the drug can be used by the target population for its intended indication in an appropriate and safe manner outside medical supervision. The US FDA recommendation, similar to other national drug regulatory bodies, is to perform an actual use study using the label developed and tested in the label comprehension studies to ensure that users understand the information about how to correctly use the drug.²⁰ Once comprehension is established, the data from an actual use study provides insight into how consumers actually understand and use the medicine. These data include any associated complications that

occur with use to demonstrate whether adverse events occur more frequently or severely when a user is not under a prescriber's care. In the context of medical pregnancy termination, this type of study would collect data on complications of the termination process such as bleeding, infection, need for an aspiration procedure, missed ectopic pregnancy and ongoing pregnancy, as well as any rarer complications, such as death.

Limited data exist from settings where women obtain mifepristone and misoprostol directly from a pharmacy. A recent, unpublished study described women's experience of medical termination self use; the authors followed women obtaining medical termination from pharmacies in Bangladesh.¹⁰ Pharmacy workers were asked to enrol women, and participants agreed to be contacted by phone before taking the pills. Of 642 eligible participants, 192 agreed to participate and 109 provided information through 15 days post-termination. The majority used the mifepristone and misoprostol combination pack (80%), and 71% of them reported correct use (mifepristone followed 24 hours later by 800 µg misoprostol). Follow up occurred 15 days later; 96% of combination pack users reported no longer being pregnant. However, some women reported symptoms on day 15 suggesting the need for medical attention, including fever (13%), heavy bleeding (10%) and bad cramping or pain (5%). Only 2% of women had sought medical attention; further data, including whether aspiration or repeated dosing of abortifacient medicines was required, are not available.

In the absence of a targeted actual use study to investigate complication rates and need to seek health care in a

Table 2. Complications following use of mifepristone and misoprostol for induced termination obtained through telemedicine services

Context	What women can do	Results	Population/ Source
Telemedicine: seeking medical termination drugs online (restrictions on service availability in country)	Recognise ongoing pregnancy	1.9% (<9 weeks) 1.7% (<13 weeks) 6.9% (>13 weeks)	Brazil ⁷
	Seek care for concerns/ complications	20.9% had a surgical intervention for the following indications: No reported complication (42%) Pain (10.9%) Heavy bleeding (12.5%) Fever (3.1%) Not enough bleeding/pain (9.4%) 1.6% had ongoing pregnancy	Global data ^{8,33}
		12.4–13.6% had a surgical intervention (indications not reported)	

population self-using medical pregnancy termination, some indicative data are available from telemedicine services through Women on Web (Table 2). Although other online fora exist, Women on Web is the only site which has published data on clinical outcomes of women after medical termination through their service. Ongoing pregnancies were reported in 1.6–1.9% of those with pregnancies <13 weeks of gestation and a surgical intervention was undertaken for 12.4–20.9% for various indications. This high rate of surgical intervention probably indicates both the need of some women to seek in-person guidance as well as overtreatment by some providers. Those with gestational ages >12 weeks were alerted by the service that they were at higher risk of adverse outcomes; almost half of them, 44.8%, required a surgical intervention and ongoing pregnancy rate was 6.9%.

Where women receive in-person follow-up appointments as standard after medical pregnancy termination in clinics, rates of non-return are high. Women with complications of termination, however, have symptoms and present for care, as is evident in Table 2. This finding is analogous to that of spontaneous termination, where women manage complications of pregnancy loss outside the medical system, albeit they are arguably less prepared for the experience of bleeding, cramping and expelling a pregnancy than women undergoing induced termination.^{28,29}

Discussion

Many aspects of women's self-use of medical pregnancy termination have been well-established; certainly the best-studied is the woman's ability to manage the termination process at home after instructions from a clinician. Although reports indicate that abortifacient drugs are increasingly available through the black market, drug sellers, or other mechanisms without medical supervision, no studies have directly investigated the implications of such access on clinical outcomes and complication rates. In addition to the possibility that actual-use medical termination outcomes may differ from those reported and studied in clinical settings, they will also differ based on the medicines available (combination versus misoprostol alone). Outcomes such as successful termination would be expected to be lower in settings where only misoprostol is available and where drug quality is not assured.³⁰ Complications will also be more common if medical termination regimens are used (off-label) at gestational ages beyond 10 weeks.

Considering the self-use of medical termination through the OTC regulatory lens clarifies where evidence gaps exist for use in the out-of-clinic setting. If we were to embark on a development programme for OTC use, the critical elements currently missing to demonstrate appropriate use

without medical supervision are label comprehension, self-selection and actual use studies. A label comprehension study would require development and iterative testing to achieve acceptable comprehension of a product label inclusive of the indication, instructions on how to use the medication, contraindications to use (including who should not use) and when to seek care from a medical professional. A self-selection study would determine whether women can use the label to determine on their own if the product is appropriate for them, which primarily depends on determination of an eligible gestational age. In addition to the evidence indicating women's accuracy in determining gestational age eligibility based on their LMP, there are now investigations of women using LMP-based gestational age calculators or applications in the developing world. Future research might explore more objective measures from urine analytes, using an as yet unknown indicator to overcome individual variability of β human chorionic gonadotrophin to develop a rapid test to calculate gestational age. The results of an actual-use study would indicate how women translate the label information into correct or incorrect use of the medicines, self-management of the termination process, side effects and complications, including when to seek medical care.

Serious complications following medical termination are uncommon in clinical studies. Although ongoing pregnancy occurs <1% of the time with mifepristone and misoprostol ≤ 10 weeks of gestation, there is ongoing investigation into how best to identify these women, whether it be symptom-based or by use of semi-quantitative^{4,31,32} or low-sensitivity^{2,3} urine pregnancy tests. The critical step for safely self-using medical termination is understanding when to seek medical care, both for signs and symptoms of ongoing pregnancy as well as for complications such as bleeding and infection, and documenting that they are able to do so. Ideally, these services include trained providers. Reports from Women on Web indicate that women may overestimate complications or require more guidance on what to expect from the termination process given that 12–20% subsequently received a surgical intervention,^{7,8,33} although this may also reflect provider overtreatment or local treatment standards. In contrast, women receiving medical termination from Bangladesh pharmacies reported low rates of seeking medical care. These outcomes would be critical in future studies, as would be done in an actual-use study.

This review focused on medical termination use up to 10 gestational weeks. Efficacy of this regimen decreases and need for surgical intervention increases as gestation advances.^{7,34} In an OTC setting, concerted research would need to determine how to best mitigate the risk of off-label use in later gestations. In self-selection studies, a critical outcome would be minimising the possibility of underestimating gestational age. Label development would need to

include a warning of the adverse consequences associated with later gestations. Finally, the likelihood and risk of misuse would be informed by an actual-use study where such labelling is used.

Requiring follow up after medical termination persists in many clinic settings, despite the high effectiveness of mifepristone and misoprostol for early gestations and specific guidelines from the World Health Organization that routine clinic follow up is not necessary.⁵ Women may be able to determine when termination is successful using a symptom-based questionnaire, as demonstrated recently. Indeed, in studies comparing women's assessments of expulsion to those made by clinicians^{35–38} or ultrasound,³⁸ when standardised questions are used,^{35–37} women have proven themselves to be nearly as accurate as clinicians at both. Using these standardised questions in self-use settings may be helpful guidance regarding termination success and for identification of when a woman might need to seek care or diagnostics to detect ongoing pregnancy.

An area of recent and ongoing efforts is the development and testing of tools to support women through the termination process. In some settings, hotlines or text messaging have been introduced and in one recent study, was demonstrated to be useful.³⁹ Women who received texts for support during home misoprostol, after mifepristone administration in clinic, had significant reductions in anxiety and stress during the termination process.³⁹ Such support mechanisms may have the potential to decrease the high surgical intervention rates seen in Gomperts' reports of women self-using medical termination and are worthy of further study in varying settings.⁴⁰

As non-traditional access to medical termination expands, the research agenda to improve and establish safe self-use has clear priorities. First, it needs to include development of an understandable label or product information which includes indication, eligibility, contraindications, how to use and when to seek medical advice. Next, this label/product information should be used to provide data on the expected outcomes and complications following self-use in a setting where such access is on the horizon. Although there may be political opposition to moving medical pregnancy termination OTC, such a regulatory change could result in significant improvements in access to early termination and deserves to be rigorously studied.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

NK conceived of, designed and wrote the review; DG contributed to the design and conduct of the review; EJ, DB and LC contributed to the conduct of the review.

Details of ethics approval

No ethical review was required for this review of the literature.

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